

Appln. No. 09/982,095
Amd. dated April 28, 2005
Reply to Office Action of November 2, 2004

REMARKS

The Office Action and the cited and applied reference have been carefully reviewed. No claim is allowed. Claims 1-4 and 6-12 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The traversal of the requirement for restriction is not found persuasive and therefore the requirement is still deemed proper by the examiner and made final. A petition for withdrawal of the restriction requirement is filed on even date with the instant amendment.

Claims 1-8 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated in part by the amendments to the claims and is also traversed in part.

Regarding claim 1, the examiner's suggested amendments to the second and third steps of assay A are adopted. In addition, applicants respectfully point out that the presently claimed method identifies molecules that mediate neuronal survival in the absence of neurotrophic factors by transactivating (not by direct activation) a neurotrophic receptor. Assay A of claim 1 is using the detection of binding of the anti-phosphotyrosine antibody to a phosphorylated form of

the neurotrophic receptor as an indicator that such transactivation is occurring because the neurotrophic receptor is being phosphorylated and activated at a tyrosine residue.

Regarding claim 4 and 8, applicants have defined neuronal cells to include PC12 cells and N2a neuroblastoma cells (see specification, page 19, paragraph [0034] and page 26, lines 1-3). Those of skill in the art recognize and understand that, for purposes of the present invention, PC12 pheochromocytoma cells and N2a neuroblastoma cells are considered "neuronal" cells (i.e., have all the characteristics of a neuronal cell line except that they are immortal), and can be used in the presently claimed assay as a surrogate for a normal neuronal cell line. For instance, the Fan et al., *Molecular Brain Research*, 132:38-50 (2004) publication, a copy of which is attached hereto, discloses in the abstract that "Using mouse neuroblastoma 2A (N2A) cells as a model system, we have found that overexpression of Dvl promotes the outgrowth of neurite-like processes, and leads to the induction of a striking, biopolar morphologic phenotype during neuronal differentiation". Likewise, the Dickey et al., *Neurosci. Lett.* 366:10-14 (2004), also attached hereto, discloses in the abstract that the application of the neurotrophin NGF to both rat primary neuronal cultures and differentiated mouse neuroblastoma 2A (N2A) cultures reliably induces expression of

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several immediate early genes linked to memory consolidation.

Dickey further discloses on page 10, right column, that the mouse neuroblastoma 2A cell line was chosen as a convenient model for expression analysis due to prior *in vivo* work with murine models and the ability to differentiate these cells into a neuronal phenotype. With respect to the PC12 cells, the attached Greene, *J. Cell Biol.* 78:747-754 (1978), publication at page 748, left column, first paragraph, teaches that PC12 cells, in response to treatment with NGF, take on many of the properties of normal sympathetic neurons. Accordingly, even though PC12 and N2a cells are tumor cells, they are neuronally-derived cells and take on the properties of neuronal cells. In fact, many of those in the art consider these PC12 and N2a cells as "neuronal" cells and would readily recognize and understand the metes and bounds of what is intended as "neuronal cells" as defined by applicants.

Regarding claim 7, this claim and other pending claims are now amended to recite "neurotrophic" receptors instead of "neurotrophin" receptors, thereby clearly encompassing the Ret receptor. Support for the recitation of "neurotrophic receptors" is found in the specification on page 17, paragraph [0030], first sentence, and a disclosure that Ret is a glial cell line-derived neurotrophic factor (GDNF) receptor is found at the bottom of page 16.

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The part of the rejection relating to claim 5 is obviated by the cancellation of claim 5 without prejudice.

Regarding the metes and bounds of "a small molecule activator", applicants respectfully direct the examiner's attention to the present specification, page 16, paragraph [0047], which teaches that small molecule activators overcome therapeutic problems involved in crossing the blood brain barrier and other problems associated with the delivery of large proteins to the centered nervous system. Paragraphs [0056] on page 32 and [0059] on page 35 disclose three small molecule activators, adenosine, CGS21680 and ZM241385 (see also page 43 on identification of "small" ligands). Therefore, one of skill in the art would readily recognize and understand what is meant by "small" molecule activator in view of the teachings in the specification (size of specifically tested small molecule activators, etc.) so that a small molecule activator can be easily selected from among the ligands listed in Table 1 on page 24 of the specification. Those of skill in the art would understand that such small molecules are of MW 1000 or less as compared to some neurotrophins which are large molecules of about 12,000 MW.

Regarding the recitation of "specific" binding, while applicants do not agree that this term is indefinite, this part

of the rejection is made moot by replacing the recitation of "specific" binding with just "binding".

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-5 have been rejected under 35 U.S.C. §102(b) as being anticipated by Clary et al., U.S. Patent 5,753,225. The examiner states that Clary teaches a method for screening for molecules in which the cell lysate of treated PC12 cells are reacted with the anti-phosphotyrosine TrkA monoclonal antibody 4G10 and where the relatively small molecule RtrkA.Ex IgG is identified to phosphorylate the TrkA receptor in the absence of neurotrophin NGF. This rejection is respectfully traversed.

Example 4 of Clary discloses that an anti-trkA antibody, RtrkA.Ex IgG, physically interacts/binds with the trkA receptor to stimulate protein tyrosine phosphorylation of the trkA receptor in the absence of NGF. However, it is quite clear that the antibody binds to trkA and directly activates the phosphorylation of the receptor. This is quite different from the present invention, in which a transactivator of a neurotrophic receptor is identified. This transactivator does not directly activate the neurotrophic receptor but rather activates it indirectly by signal transactivation as would be well understood by those of skill in the art. All references to

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"activator" in the claims are now amended to recite "transactivator" to distinguish from activators that only directly activate a receptor.

Attached hereto is a Prenzel et al., *Breast Cancer Research* 2:184-190 (2000), publication which refers to "signal transactivation" in the abstract as a "nonclassical model of signaling system cross-talk, in distinction to receptor activation induced by cognate ligands". The concept of "transactivation" was first introduced with regard to regulatory elements and sequences on nucleic acids. At the time the invention was made, signal transduction with regard to receptors was already established and well understood in the art.

Furthermore, given the specific examples of what is considered and understood to be small molecule transactivators in the specification as discussed above in the indefiniteness rejection, it is clear to those of skill in the art that an IgG antibody of Clary is not "small" in the sense of the specific examples of adenosine and other small molecules transactivators as taught in the present specification, nor is the IgG antibody of Clary a "transactivator".

Therefore, Clary cannot anticipate or make obvious the presently claimed invention. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

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In view of the above, the claims comply with 35 U.S.C.
§112 and define patentable subject matter warranting their
allowance. Favorable consideration and early allowance are
earnestly urged.

Respectfully submitted,

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By

A handwritten signature in black ink, appearing to be 'A. Yun', written over a horizontal line.

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